REMARKS

Claims 1-14, 26, 27 and 29-32 are pending and under consideration. In view of the remarks herein, Applicant respectfully requests reconsideration of the pending claims. It is noted that the Examiner failed to mention claims 26 and 27, which were still pending prior to issuance of the instant Office Action. Claim 27 was found allowable in the Office Action dated July 15, 2003, and claim 26 was rejected for being dependent upon a withdrawn claim. In the response mailed October 16, 2003, Applicant amended claim 26 to include all of the limitations of the claim from which it depended. As such, Applicant respectfully requests favorable examination of claim 26.

Rejection under 35 U.S.C. § 112, First Paragraph

Applicant respectfully traverses the rejection of claims 1-13 and 29-32 under 35 U.S.C. § 112, first paragraph, on the grounds that the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. More specifically, the Examiner alleges that the specification fails to recite other solvents that would have the effect of causing the pharmacologically active agent to remain on the skin other than the solvent ethanol.

Applicant directs the Examiner's attention to page 6, lines 18-21 of the specification, which teach:

> Volatile solvents for use in the subject compositions include alcohols such as methanol, ethanol, propanol, and isopropanol, and ketones, such as acetone. Other evaporative compounds may also find use, so long as they are compatible with other components of the pharmacological composition and topically acceptable to the majority of patients.

Applicant also submits herewith a signed declaration under 37 C.F.R. § 1.132 by the inventor, Alex Battaglia, M.D., Ph.D., stating that volatile solvents are used to dilute the gum resin of choice to effect a final desired concentration/viscosity of the composition. Following application of the composition to the skin, the volatile solvent evaporates to leave a hydrophobic coating comprised of the gum resin and the pharmacological agent. It is therefore reasonable to expect that the solvents listed above are interchangeable and that other alcohols, for example methanol

or propanol, and ketones, for example acetone, would serve the same purpose. "There is no magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.'" *In re Borkowski*, 164 USPQ 642, 646 (CCPA 1970). Thus, Applicant submits that Ethanol is used merely as an illustrative example of volatile solvents useful in the compositions of the invention.

Consequently, Applicant respectfully submits that one of skill in the art could readily use the invention commensurate in scope with the pending claims. Applicant respectfully submits that the description in the specification provides sufficient description of other solvents that would have the effect of causing the pharmacologically active agent to remain on the skin. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Rejection under 35 U.S.C. § 103

Applicant respectfully traverses the rejection of claims 1-13 and 29-32 under 35 U.S.C. §103 as allegedly being unpatentable over Goh et al., (Reference D1). The burden of proof in establishing a *prima facie* case of obviousness under § 103 clearly rests with the Patent Office. *In re Piasecki,* 745 F.2d 1468, 1472 (Fed. Cir. 1984). In establishing a *prima facie* case, the Patent Office, among other things, must show that (1) the prior are would have suggested to those of ordinary skill in the art that they should make the claimed invention and (2) that the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure." *Id.* Thus, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Further, when relying on the knowledge of persons of ordinary skill in the art, the Patent Office must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective

evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with." *In re Sang Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (citations omitted).

To date, the Patent Office has failed to provide objective evidence of any suggestion or motivation in the prior art to combine and modify the particular reference cited by the Office. Instead, the Office has simply recited elements gleaned from the reference and stated that the combination of these elements would have been obvious to one skilled in the art. It is well settled that the Patent and Trademark Office cannot pick and choose among the individual elements of ... prior art references to recreate the claimed invention. *SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887 (Fed. Cir. 1988). "Th[e] factual question of motivation is material to patentability, and [can] not be resolved on subjective belief and unknown authority." *In re Sang Su Lee* 277 F.3d at 1343-44. Without such objective evidence to combine the references, it is inferred that the references were selected with the assistance of hindsight. *In re Rouffet*, 149 F.3d at 1358. It is well-established that the use of hindsight in the selection of references that comprise a case of obviousness is forbidden. *Id.*

As stated by the Examiner on page 3 of the Office Action, "The difference between applicant's claims and the cited reference is that applicant's composition in effective amounts remain on the surface for a period of greater than six hours." Applicant submits herewith a signed declaration under 37 C.F.R. § 1.132 by Alex Battaglia, M.D., Ph.D., stating that podophyllin, the active ingredient taught by Goh et al., is toxic when left in contact with mammalian cells for a period greater than six hours. Goh et al. teach at page 18, middle right hand column, that "skin irritation including superficial erosions, pain and itch were the main side effects reported by the patients in both treatment regimens." However, of the group treated with podophyllin in ethanol (PE), four out of six patients that received a concentration of 0.25% (as compared to 0.5%) podophyllin, experienced no skin irritation. *Id.* The data presented by Goh et al., suggests that a *lower concentration* of podophyllin in ethanol may be an adequate treatment for penile warts, while significantly reducing the toxic effects of podophyllin. There is no suggestion to leave the compositions of Goh et al. on the skin for periods longer than six hours. Further, given that two of six patients treated in the 0.25% PE group did experience skin irritation, it can be expected that prolonged exposure to the lower concentration of podophyllin would cause increased skin irritation to a potentially greater number of patients. Applicant

therefore respectfully submits that without showing that Goh et al. disclose an explicit suggestion to those of ordinary skill in the art that they should increase patient exposure to podophyllin, and that doing so would reveal a reasonable expectation of success (i.e., no effects of toxicity), the Examiner has not met the burden of proof in establishing a *prima facie* case of obviousness under § 103.

The Examiner further states that "the difference between the applicant's claims and the reference is that the PB composition fails to contain ethanol." Applicant respectfully disagrees.

Goh et al. disclose that Podophyllin resin is available as podophyllotoxin (the purified compound) in 0.5% ethanolic solution (PE) or as a crude resinous extract mixture in tincture benzoin (PB), and find that PE is just as efficacious as PB, with a lower incidence of contact dermatitis. In fact, four of six patients treated with 0.25% PE did not experience any skin irritation, suggesting that a lower concentration of podophyllin helps to reduce the side effects of treatment. "The main disadvantages with the use of PB are its inconvenience...and its lesser efficacy compared with podophyllotoxin [PE]." (Goh et al., page 17, right column). Further, "our clinical experience indicated that PB can cause severe irritation." (Goh et al, page 18, lower right column). In the declaration under 37 C.F.R. § 1.132 included herein, the inventor, Alex Battaglia, M.D., Ph.D., describes the present invention and states that "a volatile solvent is used to dilute the gum resin of choice to effect a final desired concentration/viscosity of the composition. Following application of the composition to the skin, the volatile solvent evaporates to leave a hydrophobic coating comprised of the gum resin and the pharmacological agent." Therefore, the role of benzoin in PB is to keep Podophyllin in constant contact with the skin during treatment. As mentioned above, Podophyllin is toxic to mammalian skin. By removing benzoin from the treatment mixture, Goh et al. demonstrate reduced toxicity in treatment due to reduced concentrations of the toxic agent and reduced contact time with the skin.

Applicant submits that the only suggestion offered by Goh et al. is a theory that a lower concentration of PB may equally reduce contact dermatitis. However, there is no suggestion to add ethanol to PB to prepare a mixture of the individual treatments in Goh et al. to reduce toxic side effects. In fact, given the results of the study and the information provided above, adding ethanol to the PB composition is counterintuitive. The addition of ethanol would still yield a

mixture that contains benzoin. Thus, once the ethanol evaporates, the toxic agent , i.e. PB, is in constant contact with the skin. There is no motivation to add ethanol to PB at all when Goh et al. clearly observed that PE, in the absence of benzoin, is a superior treatment. Applicant therefore respectfully submits that without showing that Goh et al. provde an explicit suggestion to those of ordinary skill in the art to combine ethanol and PB as a therapeutic composition, and that doing so would reveal a reasonable expectation of success, the Examiner has not met the burden of proof in establishing a *prima facie* case of obviousness under § 103.

It is noteworthy to mention that the cited reference was brought to the attention of the Examiner in an Information Disclosure Statement filed on March 29, 2002. Applicant was fully aware of the work by Goh et al., as evidenced by the specification at page 2, lines 19-28, and knew that podophyllin resin is toxic and must be removed by rigorous washing 1 to 6 hours post-application. The compositions and methods of the subject invention entirely avoid the problems addressed by Goh et al. by teaching the use of pharmacological agents that are efficacious without being locally or systemically toxic or caustic to the skin of the patient. Applicant's claimed compositions are intended to remain at the site of application for at least 6 hours and more often 6 to 72 hours depending on the treatment. Accordingly, Applicant respectfully requests withdrawal of the rejection under § 103.

In view of the above remarks, it is submitted that the claims are in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application. Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

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